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COMPARATIVE NUCLEOPHILIC SUSCEPTIBILITY OF SELECTED PHOSPHORO- AND PHOSPHONOTHIOLATES BY SEMI-EMPIRICAL MOLECULAR ORBITAL CALCULATIONS

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13. ABSTRACT *(Maximum 200 words)*

The electronic properties of several phosphorothiolates were compared against the target molecule O-ethyl-S-(2-diisopropylaminoethyl)-methylphosphonothiolate (VX) by hierarchical clustering techniques and electrostatic potential maps to determine the best match for nucleophilic attack. Semi-empirical calculations and geometry optimization were accomplished with the MNDO algorithm in MOPAC v5.0. Graphical display of structures and electrostatic potentials were produced, using the Chemometric and Biometric Modeling (CBM) Branch's Molecular Modeling, Analysis and Display System (MMADS). The pattern recognition program ARTHUR was used to predict the hierarchical clustering of the electronic properties using Euclidean distance criteria. Both hierarchical clustering and electrostatic potential differences contouring predict that the molecule O-ethyl S-ethyl methylphosphonothiolate most closely resembles VX in susceptibility to nucleophilic displacement.

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PREFACE

The work described in this report was authorized under Project No. 1C162622A553F, CB Decontamination and Contamination Avoidance. This work was started and completed in April 1990.

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COMPARATIVE NUCLEOPHILIC SUSCEPTIBILITY
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1. INTRODUCTION

1.1 Problem Definition.

O-ethyl-S-(2-diisopropylaminoethyl)-methylphosphonothiolate (VX) (Figure 1) is a potent inhibitor of the enzyme acetylcholinesterase (AChE). The inhibition mechanism involves phoshorylation of the esteratic site in the enzyme. Because of the lethal toxicity of VX, severe restrictions have been placed on its use in laboratory experimentation.

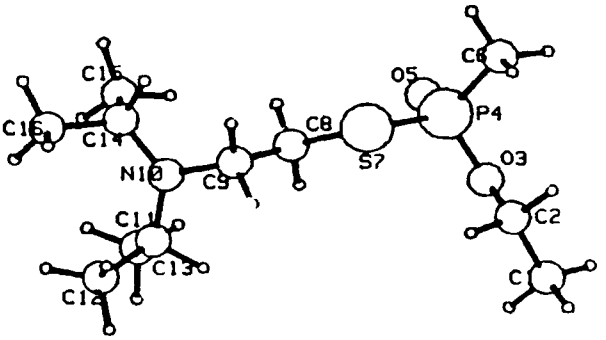


Figure 1. VX

In an effort to circumvent many difficulties involving the use of chemical agents in the laboratory, the U.S. Army Chemical Research, Development and Engineering Center (CRDEC) has been the lead organization for the development and use of chemical agent simulants (conversation with William White, Research Directorate, CRDEC, May 1990). Simulants are chemical compounds that possess similar properties and/or activities as an agent but are non-toxic. In this way, simulants will behave similarly to agents in a given experiment but require none of the precautions associated with the use of toxic chemicals. To promote the use of simulants and provide a centralized location to find properties regarding simulants, CRDEC created, as well as maintains, the Chemical Agent Simulant Data Center.[1]

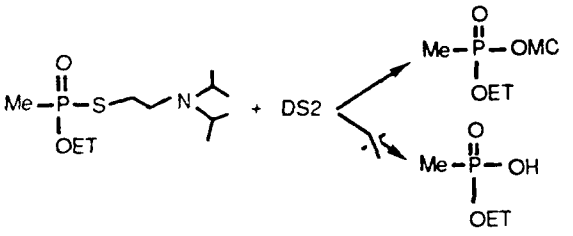
One area with little success in developing simulants has been in simulating reactivity, either oxidative or hydrolytic. This study will present a new approach to examining this problem.

1.2 Potential Simulants.

Figures 2-8 display the potential simulants that have been examined in this study. The compounds examined with the exception of O-ethyl-S-ethyl methylphosphonothiolate (EA-5533) (Figure 5) are common pesticides.[2] Research Directorate, CRDEC, (conversation with Leonard Szafraniec, Research Directorate, CRDEC, May 1990), synthesized EA-5533.

1.3 Nucleophilic Displacement In VX.

VX detoxification can cause a number of different mechanisms. This study will focus only on the nucleophilic displacement of the alkylthio group by a nucleophilic attack at the phosphorus. The products obtained by this attack are a function of the strength of the nucleophile, pH, and solvent. The VX reaction with DS2 (sodium hydroxide, methoxyethanol, diethylenetriamine) involves the substitution of the 2-(bis-isopropylamino) ethylthiol group by the 2-methoxyethoxide (OMC) (equation 1). In water/alcohol solutions, competitive substitution by the alcohol can occur (equation 2).[3]



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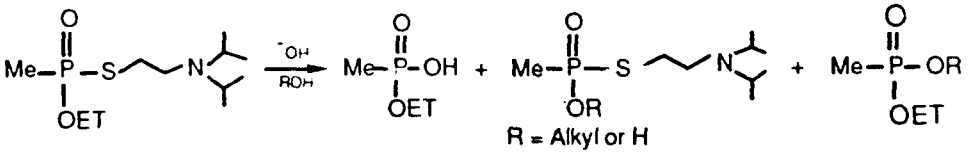

(2)

1.4 Theoretical Chemistry Applications.

Computational chemistry is extensively used in the examination of chemical compound properties. Although a number of computational methods have been used successfully to predict physical and biological properties, prediction of chemical reactivity has been less successful.[4,5,6] Theoretical methods allow for the facile computation of numerous electronic properties of

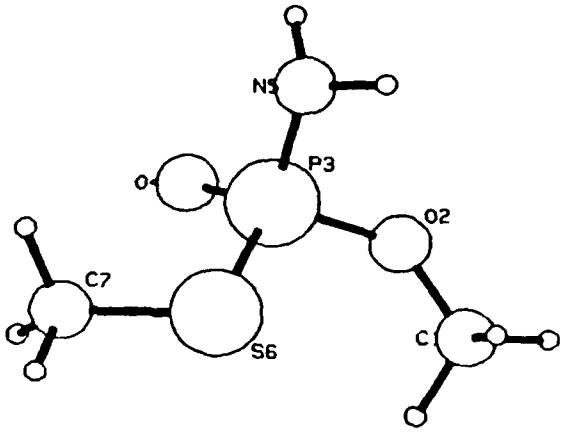

Figure 2. Simulant 1, O-Methyl-S-Methyl Aminophosphorothiolate

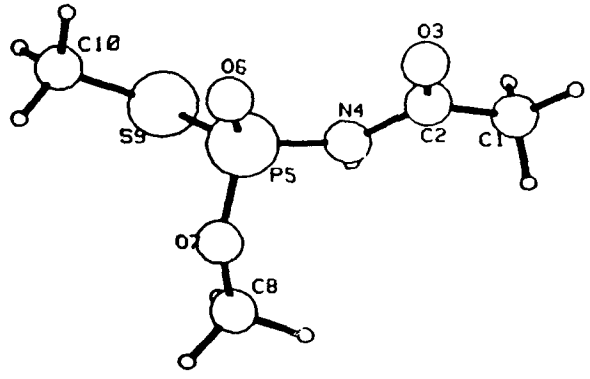

Figure 3. Simulant 2, O-Methyl-S-Methyl-N-Acetyl Amidophosphorothiolate

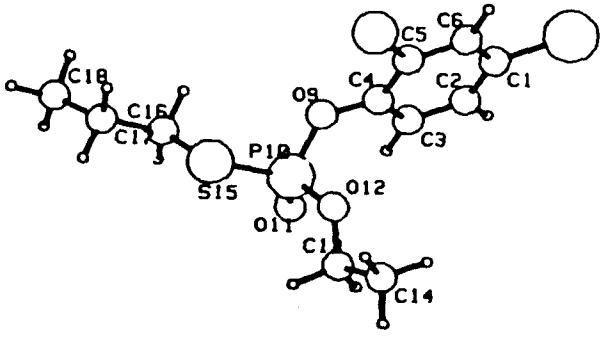

Figure 4. Simulant 3, O-Ethyl-O-Chloro-Bromophenyl-S-Propyl Phosphorothiolate

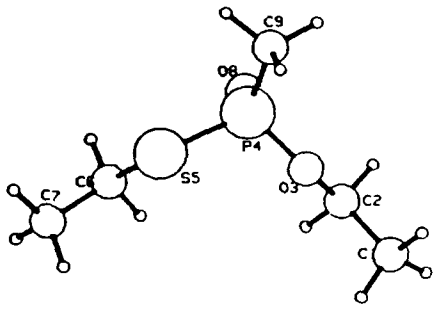

Figure 5. Simulant 4, O-Ethyl-S-Ethyl Methylphosphonothiolate

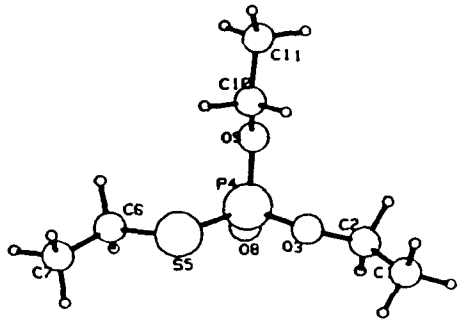

Figure 6. Simulant 5, Bis(O-Ethyl)-S-Ethyl Phosphorothiolate

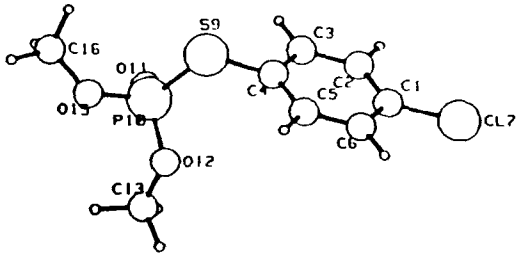

Figure 7. Simulant 6, Bis(O-Methyl)-Chlorophenyl Phosphorothiolate

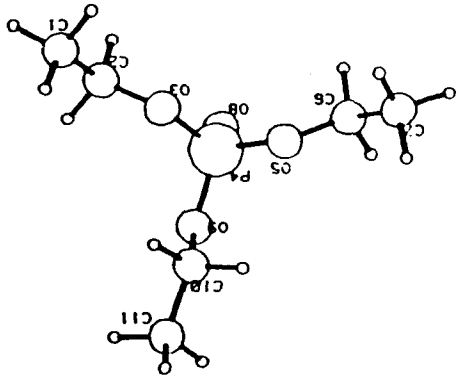

Figure 8. Simulant 7, Triethyl Phosphate

molecules that can be used to infer reactivity and used to further compute reaction related properties. In effect, the ground state electronic and steric attributes are used to qualitatively predict how well a reaction can occur.

One difficulty in the application of molecular orbital calculations is the sheer amount of electronic data that can be generated. Two approaches to apply molecular orbital calculations have been examined in this study. The first approach uses hierarchical clustering techniques to find the compound that best matches those electronic properties expected to influence the nucleophilic displacement. In the second approach, molecular graphics have been applied to condense the plethora of numerical data into an easier to comprehend description of the electrostatic potential. The electrostatic potential has been used successfully in this laboratory and by others to qualitatively assess the reactivity of a substrate.[*,7]

2. COMPUTATIONAL PROCEDURE.

All geometry optimizations and calculations of electronic properties have been performed using the MNDO algorithm as contained in MOPAC v5.0 on a Stardent Titan super workstation.[8,9] Graphical display of the electrostatic potentials and molecular structures were done using the Molecular Modeling Analysis and Display System (MMADS) program.[10] The pattern recognition program, ARTHUR, was used to perform all hierarchical clustering.[11]

3. RESULTS AND DISCUSSION

Two methods were employed to determine if theoretical and computational methods could be useful in selecting simulants. If the important properties that determine the reactivity of VX with respect to nucleophilic displacement could be adequately matched by a potential simulant, then the reactivities would likely be similar. However, the important properties in hydrolysis were not intuitively clear. Seven theoretically determined electronic properties were calculated and used to attempt to model reactivity (described in section 3.1). Using pattern recognition methods, it is possible to determine which of the potent simulants best match all or some of the electronic properties of the agent. A second approach using the molecular electrostatic potential (MEP) was also employed. In particular, the difference between the MEP of the simulant and VX was examined. The reactivities will more likely be similar as the MEP map approach exact overlap.

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*Famini, George R., "A Computational Comparison of the Electronic Properties of G Agents with Selected Reaction Simulants," In Proceedings of the 1989 Scientific Conference on Chemical Defense Research, CRDEC-SP-024, U.S. Army Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, MD, September 1990, unpublished data.

3.1 Hierarchical Clustering.

The electronic properties, calculated by the MNDO algorithm, expected to contribute to the electrophilic properties in VX are as follows:

- heat of formation,
- the energy of the highest occupied molecular orbital,
- the energy of the lowest unoccupied molecular orbital,
- the electronic charge of the phosphorus,
- the electronic charge of the sulfur atom,
- the electronic charge of the P = O oxgyen, and
- the dipole moment.

These electronic properties, the values for VX, and the seven simulants are listed in Table 1.

Three dendrograms were produced by the pattern recognition package ARTHUR. The first dendrogram (Figure 9) compares all seven electronic properties for VX and the simulants. The dendrogram shows that Simulant 4, O-ethyl-S-ethyl methylphosphonothiolate is the best fit for VX. Simulants 3, 6, 5, and 1 are the second best choices; Simulant 2 is the third best choice. A second dendrogram (Figure 10) compares six (the heat of formation was not considered) of the Modified Neglect of Diatomic Differential Overlap (MNDO) electronic properties for VX and the simulants.

Simulants 1, 3, 4, 5, and 6 were the first choice for the best fit and Simulant 2 the second choice. A third dendrogram compares only the energy of the orbit (ELUMO), because the Frontier Molecular Orbital Theory predicts that this property is the most significant in Sn2 chemistry. For the ELUMO dendrogram (Figure 11), the ranking is Simulant 4 followed by Simulant 1 for the best fit for VX.

3.2 Electrostatic Potentials.

Electrostatic potentials have been shown to be a good indicator of relative reactivity due to attraction and repulsion of point charges. The Molecular electrostatic Potential (MEPs) were calculated using a modified coulombic expression as shown in equation 3.

$$V_{app} = \sum_{A} \frac{q_a}{R_A - r} \qquad (3)$$

V_{app} is the approximate electrostatic potential
q_a is the formal charge on atom A
R_A is the position of the atom
r is the electron at point r

Electrostatic potentials for VX and the simulants are shown in Figures 12-19. The planes displayed are the phosphorus, the double bonded oxygen, and the leaving group. The significant region of the plot is the area

Table 1. MNDO Electronic Properties

Compound	H	Ehomo	Elumo	qP	qO	qS	DM
VX	-88.27250	-9.30036	-1.73961	.8413	-.5898	-.1487	3.606
1	-90.44274	-10.44339	-1.93622	.9973	-.6014	-.0850	3.270
2	-129.02166	-10.41193	-2.15472	1.0980	-.5520	-.1365	6.104
3	-123.78412	-9.44083	-2.30574	1.0757	-.6325	.0108	1.667
4	-103.26889	-10.10178	-1.63999	.8195	-.6320	-.0890	1.850
5	-154.70651	-10.50167	-2.03172	1.0823	-.6091	-.0437	3.005
6	-115.91889	-9.80965	-2.23556	1.0490	-.6367	.0927	1.788
7	-209.08610	-11.11833	-0.83351	1.3962	-.6400	-.4998	2.918

H = Heat of formation
Ehomo = Energy of the highest occupied molecular orbital
Elumo = Energy of the lowest unoccupied molecular orbital
qP = Charge on the phosphorus atom
qO = Charge on the oxygen atom
qS = Charge on the sulfur atom
DM = Dipole moment

Simulant 1, O-Methyl-S-methyl aminophosphorothiolate
Simulant 2, O-Methyl-S-methyl-N-acetyl amidophosphorothiolate
Simulant 3, O-Ethyl-O-chlorobromophenyl-S-propyl phosphorothiolate
Simulant 4, O-Ethyl-S-ethyl methylphosphonothiolate
Simulant 5, Bis(O-Ethyl)-S-ethyl phosphorothiolate
Simulant 6, Bis(O-methyl)-chlorophenyl phosphorothiolate
Simulant 7, Triethyl phosphate

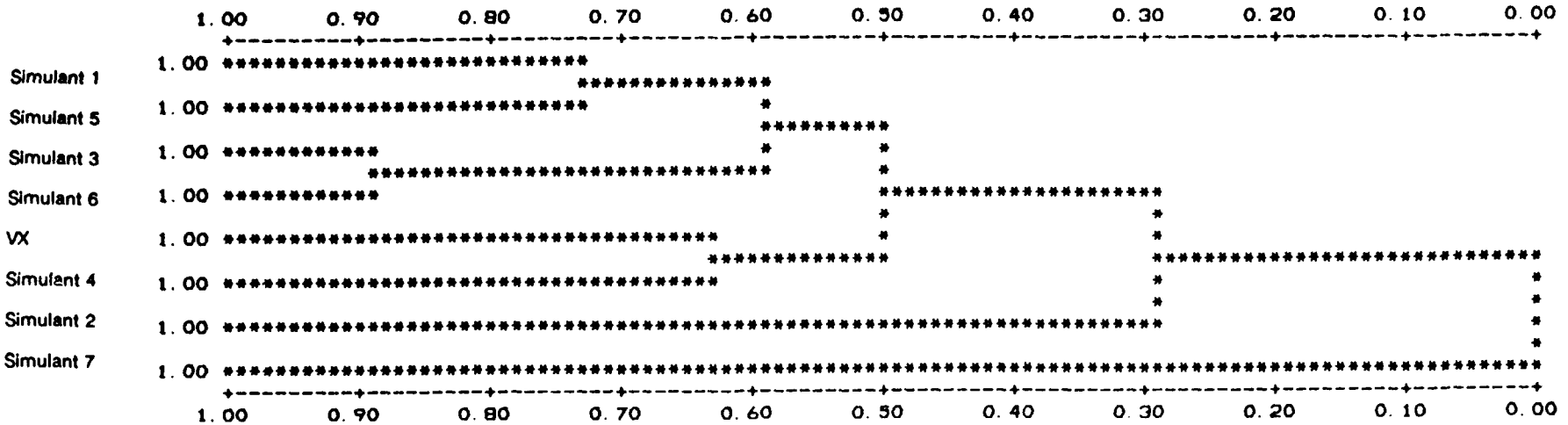

Figure 9. Dendrogram for Seven Electronic Properties

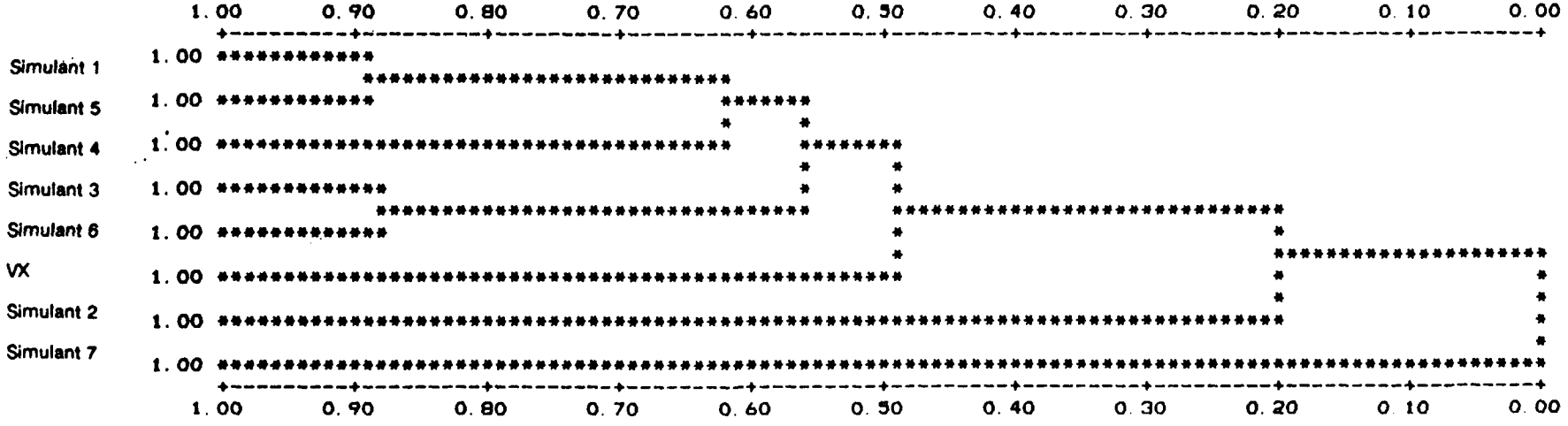

Figure 10. Dendrogram for Six Electronic Properties

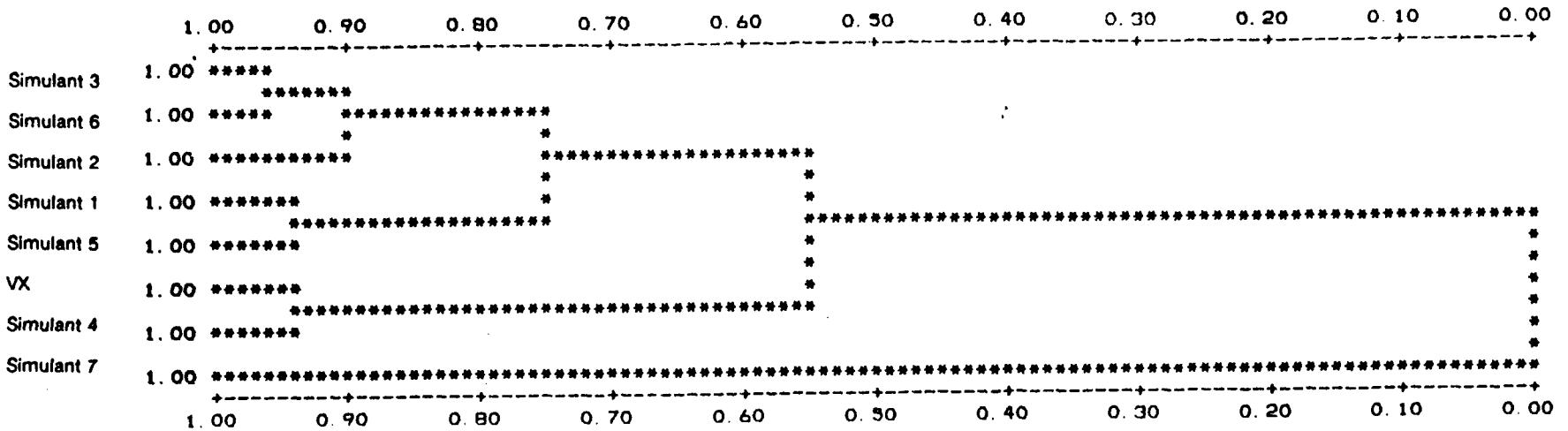

Figure 11. Dendrogram for One Electronic Property

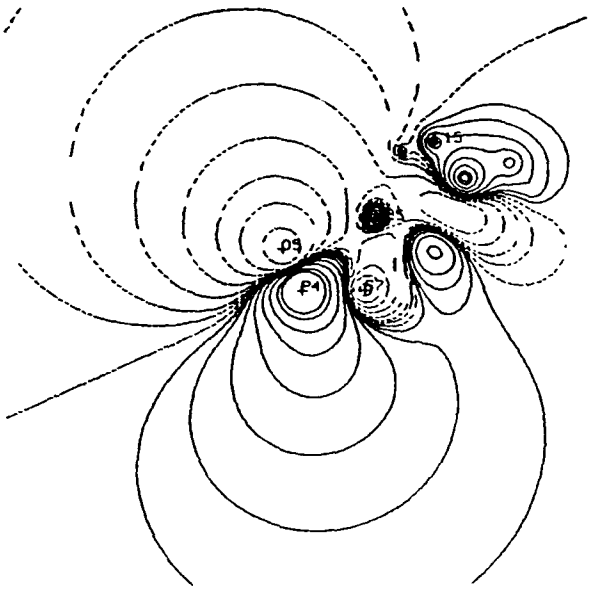

Figure 12. Electrostatic Map/VX

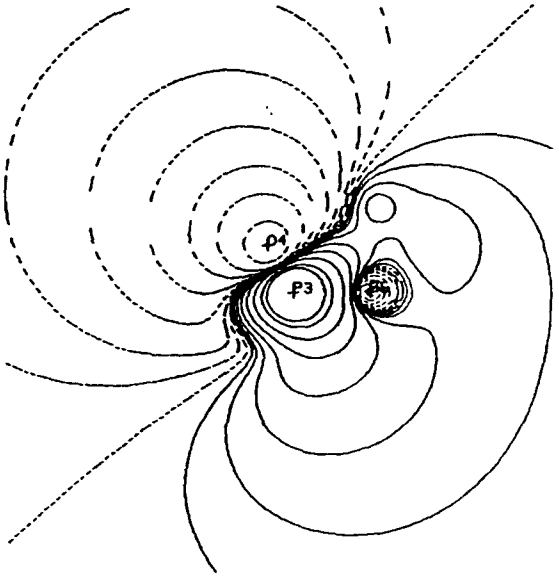

Figure 13. Electrostatic Map/Simulant 1

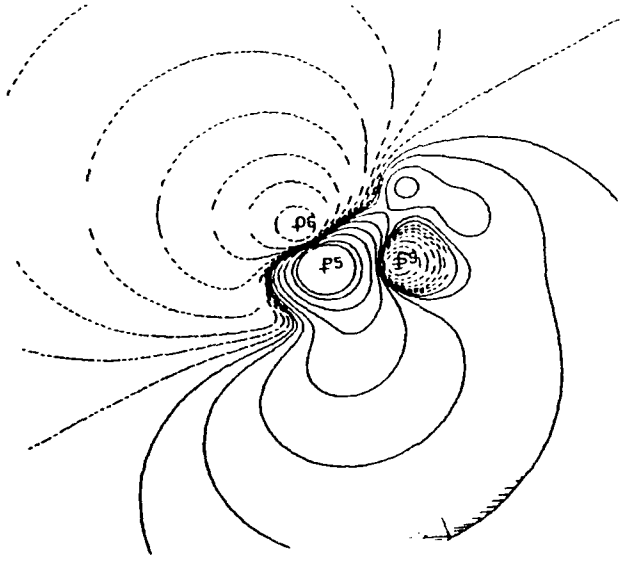

Figure 14. Electrostatic Map/Simulant 2

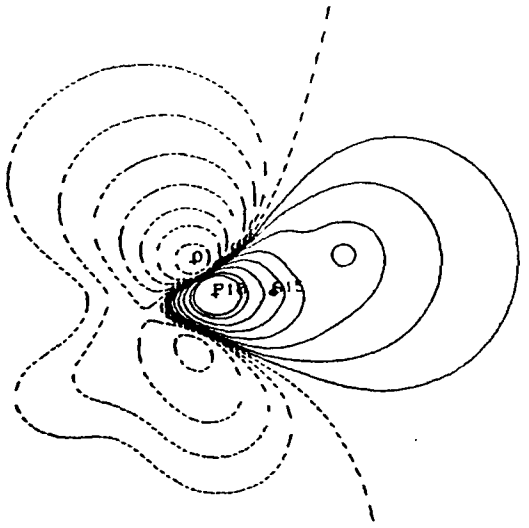

Figure 15. Electrostatic Map/Simulant 3

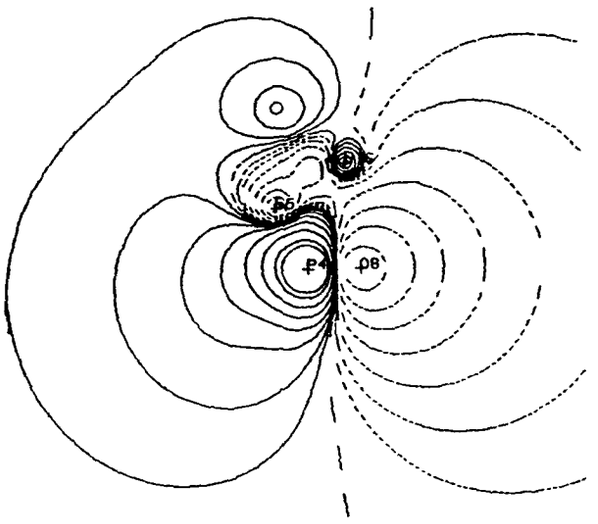

Figure 16. Electrostatic Map/Simulant 4

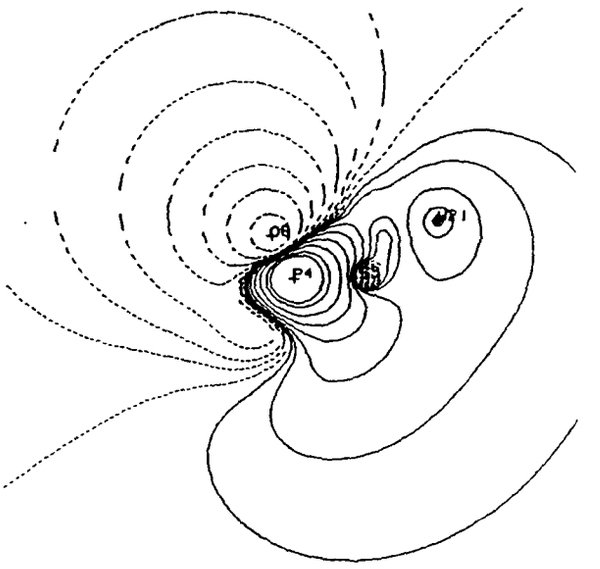

Figure 17. Electrostatic Map/Simulant 5

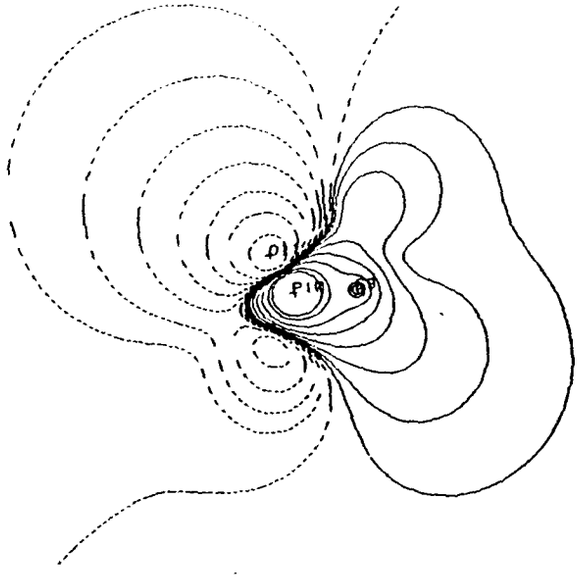

Figure 18. Electrostatic Map/Simulant 6

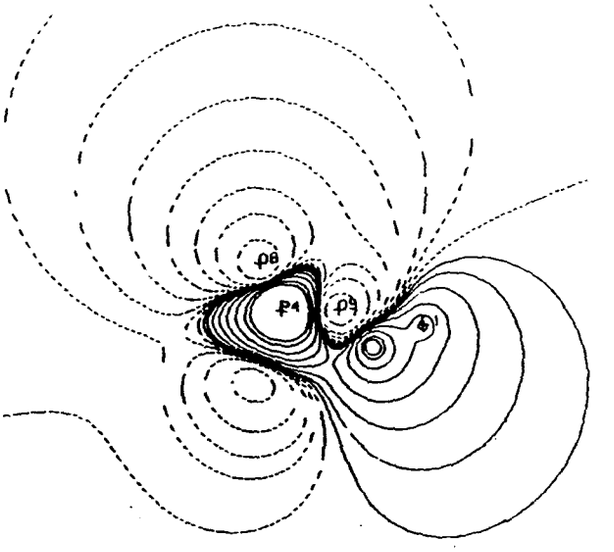

Figure 19. Electrostatic Map/Simulant 7

180° to the leaving group. This significant region is shown as solid contour lines and represents a positive area attractive to a negative charge. Simulants that best fit the reactivity of VX will have a positive region similar in shape and size.

Computer generated electrostatic potential difference maps have been made between VX and each of the simulants, thus simplifying the comparison. The simulants that have the best electrostatic overlaps will result in difference maps with the smallest positive lobe opposition to the leaving group. The electrostatic overlap maps are shown in Figures 20-26.

Examination of the diffence map (Figure 23) shows that Simulant 4, O-ethyl-S-ethyl methylphosphonothiolate, would closely resemble VX in nucleophilic reactivity. However, Simulant 1, O-methyl-S-methyl aminophosphorothiolate, and Simulant 5, O-ethyl-O-ethyl S-ethyl phosphorothiolate (Figures 20 and 24, respectively), may provide reasonable reactivity.

Simulant 4 (EA-5533) and Simulant 5 were compared (Figure 27) to determine the difference in phosphorus reactivity between a phosphonothiolate and a similar phosphorothiolate. The large positive lobe shown indicates a large difference in reactivity between the two phosphorus.

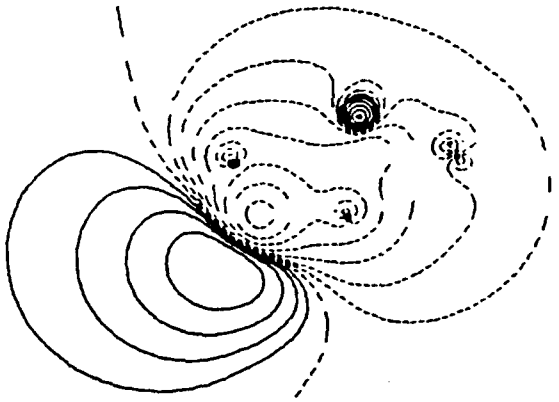

Figure 27. Difference Map/Simulant 4 and Simulant 5

4. SUMMARY

Hierarchical clustering and electrostatic potential techniques were used to predict the similarity in reactivity between several potential phosphorothiolate simulants and VX. The technique considered the Sn2 displacement of a leaving group attached to phosphorus. Two compounds, O-methyl-S-methyl aminophosphorothiolate and O-ethyl-S-ethyl methylphosphonothiolate were identified as suitable simulants. Table 2 summarizes the ranking of simulants for MEP and hierarchical clustering.

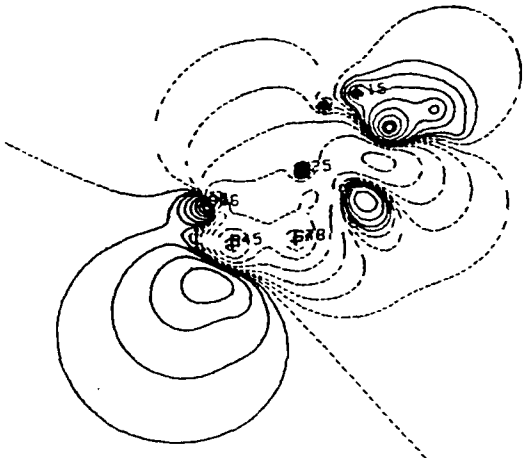

Figure 20. Difference Map/VX and Simulant 1

Figure 21. Difference Map/VX and Simulant 2

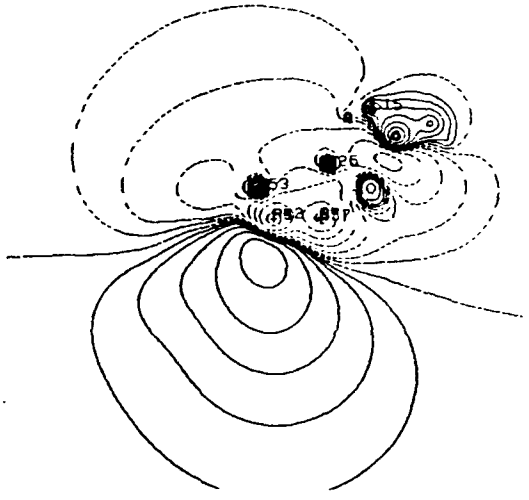

Figure 22. Difference Map/VX and Simulant 3

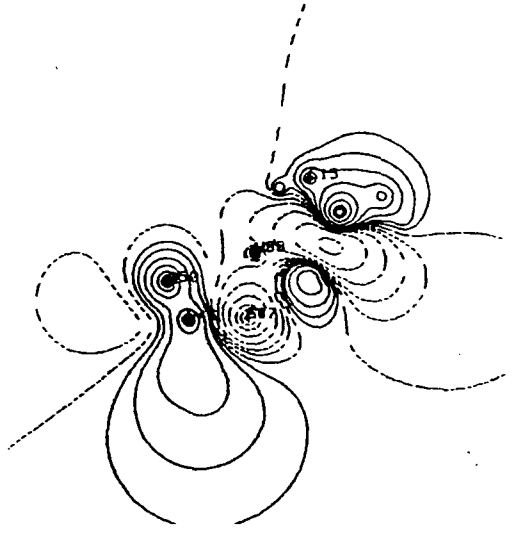

Figure 23. Difference Map/VX and Simulant 4

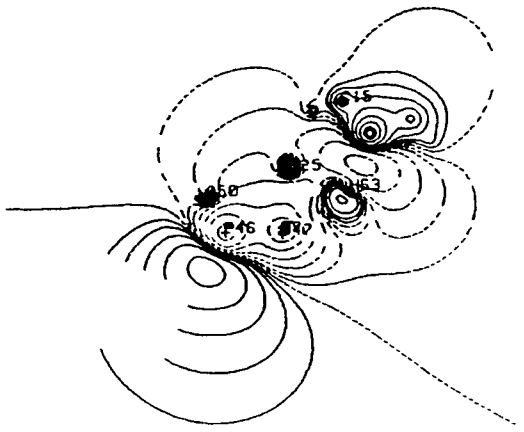

Figure 24. Difference Map/VX and Simulant 5

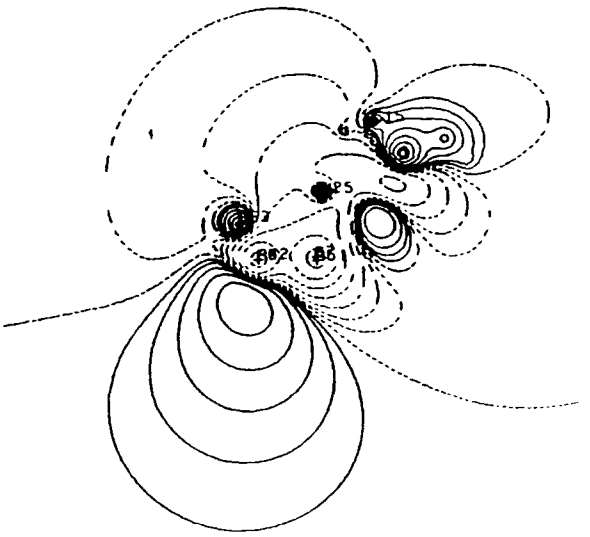

Figure 25. Difference Map/VX and Simulant 6

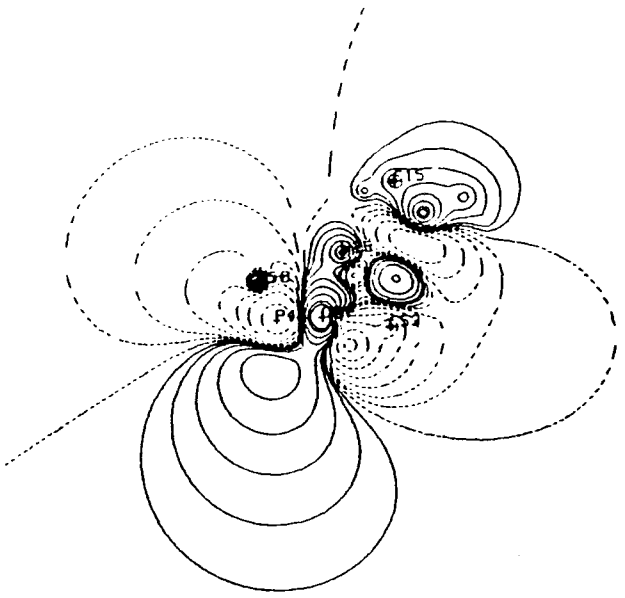

Figure 26. Difference Map/VX and Simulant 7

Table 2. Simulant Ranking

Heirarchical Clustering

Rank	7 Electrostatic Properties	6 Electrostatic Properties	1 Electrostatic Property	MEP
1	simulant 4	simulants 1,3, 4,5,6	simulant 4	simulant 4
2	simulants 1,3, 5,6	simulant 2	simulants 1,2,3,5,6	simulant 1

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